BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/014,096	02/04/93	HUSTON J	CRP-008DV(20

ULM, J EXAMINER

18N2/0708

PATENT ADMINISTRATOR
TESTA, HURWITZ & THIBEAULT
53 STATE STREET
BOSTON, MA 02109

ART UNIT	PAPER NUMBER
1812	21

DATE MAILED: 07/08/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/26/93 and 2/9/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 27 to 38 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 27 to 38 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Claims 27 to 38 are pending in the instant application. Claim 27 has been amended as requested in Paper Number 18. Claims 1 to 26 and 39 to 46 were canceled as requested during the prosecution of parent application Serial Number 07/661,070, now abandoned.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 27 to 38 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Cousens et.al. patent (1A, of record) in view of the Cohen et.al. patent (1B, of record). These claims are drawn to a fused polypeptide comprised of a leader sequence that facilitates purification, a cysteine-free hinge region, a selected cleavage site at the carboxyl terminal of the hinge region, and a target polypeptide. The Cousens et.al. patent clearly described the construction of a fusion protein in which the two primary components were joined by a flexible linker to facilitate separation of those components prior to the instant invention. Applicant has traversed this rejection by alleging that the Cousens et.al. parent application Serial Number 06/717209 ('209) does not suggest "that a hinge region and cleavage site may be engineered between the leader sequence and target polypeptide of a fusion protein so as to give preferential cleavage of the hinge region cleavage site." Applicant is incorrect. The '209 reference clearly describes the construction of a fusion protein consisting of two components separated by the

flexible linker -Ser-Thr-Ser-Thr-Ser-Thr-Ser-, which is preceded by a serine protease cleavage site. Applicant has indicated that this reference does not explicitly teach that this linker constitutes a flexible linker which promotes cleavage of the fusion protein, but has ignored the fact that these features are implicit in this reference. It is inconceivable that Cousens et.al. or any artisan with a working knowledge of protein chemistry would not have known that the chosen linker was flexible and, since Cousens et.al. synthesized this linker "from scratch", then it is clear that they intentionally chose to join the components of their fusion protein with a flexible linker.

Additionally this reference described the construction of fusion proteins without flexible linkers adjacent to their cleavage sites. Again, an artisan would have recognized the motive behind the use a the flexible linker without it being explicitly stated. Those fusion proteins described in this reference which contained chemical cleavage sites and which were to be cleaved by cyanogen bromide did not contain such linkers whereas those fusion proteins which were designed to be cleaved enzymatically by a serine protease included these linkers. Clearly, the Cousens et.al. application described the incorporation of a flexible linker (a.k.a. hinge region) into the cleavage site of a fusion protein to eliminate potential steric hindrance that would have otherwise made the cleavage site unavailable or less available to a relatively large molecule such

as a protease and the exclusion of such linkers from those fusion proteins that were to be cleaved by the much smaller molecule cyanogen bromide. There is no doubt that the flexible linker described in this reference was incorporated into a fusion protein to facilitate cleavage of that protein.

The position of the cleavage site is a matter of experimental design choice that would have been obvious to an artisan prior to the instant invention. The utilization of a cleavage agent and its respective site which allows for the production of a mature protein with an authentic amino or carboxyl terminus residue was old and well established in the art prior to the making of the instant invention.

The Cohen reference shows that it was known in the art of fusion protein construction that "the elimination of cysteine residues in the leader peptide [of a fusion protein] prevents possible interactions and interferences with the obligatory formation of disulfide bridges in the active analogs" (the target polypeptide). To construct a fusion protein like the one described in the Cousens reference without cysteine residues in the hinge region as advised in the Cohen et.al. patent was fairly taught in the art prior to the making of the instant invention.

Any inquiry concerning this communication should be directed to John D. Ulm at telephone number (703) 308-4008.

John D. Ulm
Patent Examiner
Art Unit 1812